

## Comparing neurocognitive function in individuals receiving chronic methadone or buprenorphine for the treatment of opioid dependence: A systematic review.

Duncan Hill<sup>1,2</sup>, Daniel Garner<sup>3</sup>, and Alex Baldacchino<sup>3,4</sup>

1. Addictions Services, NHS Lanarkshire, Motherwell, Scotland, UK

2. Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, Scotland, UK

3. School for Medicine, University of St Andrews, Fife, Scotland, UK

4. NHS Fife, Queen Margaret Hospital, Whitefield Road, Dunfermline, Fife, Scotland, UK

### Summary

**Introduction:** Agonist Opioid Treatments (AOT) have been, in comparison to healthy controls, associated with neurocognitive impairment in different domains. This review identifies differences in neurocognitive function as a result of treatment with either buprenorphine or methadone. **Method:** A qualitative and systematic literature review of published articles from 1946 to 29/2/2016 on neurocognitive function of patients prescribed buprenorphine or methadone and compared with healthy patients utilising the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. **Results:** The limited data demonstrate buprenorphine as presenting with fewer neurocognitive impairments, in cognitive impulsivity, cognitive flexibility and attention domains when compared with methadone. However both treatments modalities presented with more impairments in neurocognitive function domains, including short term memory, attention, cognitive flexibility, cognitive impulsivity, motor impulsivity and non planning impulsivity, when compared with healthy control groups. **Discussion:** The lack of published papers in comparing neurocognitive impairment between the treatment modalities limit interpretation of this systematic review. **Conclusion:** Further methodologically rigid and higher quality research into the neurocognitive effects of these treatment modalities in the opioid dependent populations, especially when in treatment, is urgently required.

**Key Words:** Neurocognitive Impairment; buprenorphine; methadone; treatment; opioid dependence

## 11. Introduction

Treatment for opioid (and opiate) addiction using agonist opioid treatments (AOT) (i.e. methadone and buprenorphine) have been associated with neurocognitive impairment in comparison to healthy controls.

For the purposes of this review we will use the term opioids to encompass both opiates and opioids. Opioids are widely used both legally in treatment, for their analgesic effects, and illicitly, for the psychotropic effects. The neurocognitive impairments associated with opioid use have already been documented [4]

Opioids are known to alter receptor sensitivity and expression, demonstrating a tolerance effect, but

also display psychological dependence by altering the brains behavioural circuits. The receptors affected by opioids, are located through the brain and spinal cord, including the thalamus, hypothalamus, hippocampus, amygdala and the cerebral cortex [12], which are important for neurocognitive function, but are also connected to the reward and reinforcement area in the brain, the nucleus accumbens.

Opioid use has been demonstrated in the brain to increase oxidative stress, which contributes to neurotoxicity leading to neurocognitive impairment [7, 33].

In the review by Büttner and Mall, they noted reduced neuronal density in majority of patients dying from heroin overdoses due to respiratory depression and associated brain hypoxia [6].

Consideration of other contributing factors other

than the direct opioid toxic effects on neurocognitive impairment needs to be considered. This can include bacterial and viral infection and other potential neuropathological insults [10]. These factors will not be reviewed in this systematic review.

To measure neurocognitive function in individuals the precise function being tested must be defined. Muriel Lezak, the author of the first book exploring neuropsychological assessment, wrote 'Direct observation of the fully integrated functioning of living human brains will probably always be impossible' [18]. Therefore, to assess neuropsychological function in the context of assessment, three domains (and subsequent sub-domains based on neurocognitive tests) need to be clearly defined to allow the objective observation of neurocognitive function in individuals:

- Intelligence
- Executive Function
- Memory and Learning

The use of an intelligence assessment allows an estimate the premorbid IQ of an individual. A vocabulary test is the primary assessment method use, e.g Shipley Institute of Living Scale (SILS) or Wechsler Adult Intelligence Scale – Revised & III [31, 38].

High level neurocognitive functions, known as Executive functions, allow for the control of behaviour to achieve a targeted outcome, this includes cognitive flexibility, cognitive planning, cognitive impulsivity, working memory and attention [5, 11, 36].

Memory and learning assesses an individual's

ability to recall and make new memories. The Atkinson-Shiffrin model of memory proposes three distinct 'stores' of memory: sensory memory (lasting a few milliseconds: providing a buffer for sensory information and allows us to address information when required), short-term memory (lasting 12-30 seconds without rehearsal: primarily auditory in nature, can store around seven chunks of information for a few seconds without rehearsal [22] duration of storage can be increased with the use of a phonological loop), and long term memory which can be indefinite (ability to store information for a lifetime [2] and can be further split into declarative memory requiring conscious thought and procedural memory requiring no thought).

A recent meta analysis looking at the effects of chronic methadone use identified global impairments in neurocognitive function relative to healthy participants [5].

This article aims to determine if there are differences in the effects on the neurocognitive function of patients being treated with either buprenorphine or methadone.

## 12. Methods

### 12.1. Literature Search

A literature review identified articles relating to the neurocognitive effects of either buprenorphine

**Table 1:** Inclusion and exclusion criteria for studies used in the review

Inclusion	Exclusion
Participants aged eighteen or over with chronic opioid dependence and currently engaged in an opioid maintenance programme	Cohorts with current uncontrolled poly-drug use (nicotine excluding).
Individuals needed to be compared to either healthy controls, abstinent individuals or another maintenance programme (methadone vs. buprenorphine) through the use of validated neuropsychological assessments.	Cohorts with a diagnosis of any Axis-1 psychiatric illness (excluding substance related disorders) as defined by DSM-IV/V (American Psychiatric Association 2000; American Psychiatric Association 2013).
Neuropsychological assessments needed to be identified and validated to allow for them to be classified into domains. If novel assessments were used a description of the cognitive functions assessed was used to classify by comparison to a defined assessment.	Cohorts with previous serious head injury.
Identified papers need to be of adequate quality matching the control/abstinent group to the maintained cohort, matching criteria should include: age, sex, years of education and years of heroin dependence	Articles with poor quality methodology,
Papers needed to report separate results for each cohort and test, papers which combined maintenance cohorts were excluded as it was not possible to extract the results required.	Cohorts including participants who were HIV serotype positive

**Table 2:** Search Subject Headings

opioid related disorders OR	AND	neuropsychological tests/impairments/deficits	AND	methadone OR
substance related disorders OR		OR		buprenorphine OR
chronic drug dependence OR		neurocognitive tests/deficits/impairments		Subutex OR
substance withdrawal syndrome				Suboxone

or methadone on patients receiving Agonist Opioid Treatment (AOT) for opioid dependence. The cohorts chosen where either direct comparison between individuals treated with methadone or buprenorphine or those compared against a healthy control group. The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were employed and the inclusion and exclusion criteria used have been tabulated in Table 1.

An electronic based search using a number of databases and incorporating articles published from 1946 to 29/2/2016 were used. The databases used where Ovid MEDLINE (1946 to 29/2/2016); EMBASE (1974 to 29/2/2016); PUBMED (1964 to 29/2/2016); PsychINFO (1980 to 29/2/ 2016). There were no language constraints employed.

The articles were identified using the search headings in Table 2.

The search terms ‘neuropsychological tests’ and ‘neurocognitive tests’ were then replaced with the sub-titles of neurocognitive domains e.g. Short Term Memory, Long Term Memory, Attention, Cognitive Flexibility, Cognitive Impulsivity, Motor Impulsivity and Non-Planning Impulsivity.

As this article is a literature review there was no requirement for ethical approval in relation to the study.

## 13. Results

### 13.1. Data analysis and study detail

The literature search provided very few articles published on the comparison of effects of treatment on the neurocognitive function of patients being treated with buprenorphine or methadone.

With the very limited number of published articles offering direct comparisons (3 articles identified) between buprenorphine and methadone, a wider but indirect comparison of the effects on neurocognitive

function were used from articles comparing either of the two therapeutic intervention against a healthy patient control group. The results of these studies were used to comment on the potential for neurocognitive impairment from the treatment with ORT against a control group.

### 13.2. Assessment of study quality

The vast majority of selected articles for this review were assessed as fair in quality using the NIH Quality Framework for case-control studies (Table 3) (NIH 2014) with others ranging in quality from poor (2 articles) to good (1 article). All studies were observational case control studies.

### 13.3. Number of articles identified

The initial literature search identified 426 articles from literature and other sources. Once duplicates were removed the total number of relevant manuscripts was reduced to 179. Titles and abstracts of 31 articles included in the accepted abstracts were screened for eligibility with an additional six articles included in the full text screening (Figure 1: QUORUM). The full text of the remaining 36 articles was assessed using the inclusion and exclusion criteria on Table 1. This assessment excluded a further 20 articles which failed to meet the inclusion criteria in the full text with the remaining 16 articles included in this review.

### 13.4. Cohorts identified

The included articles described results from the direct comparison of 60 buprenorphine maintained individuals to 74 methadone maintained individuals from 3 published articles. When the search was extended to compare either methadone or buprenorphine maintained patients to a healthy control, there

**Table 3:** Characteristics of articles identified comparing methadone maintenance patients to healthy controls.

			Methadone Group										Healthy Controls					
Study	Country	Qual-ity	N	Mean Age (yrs)	Sex (nM/nF)	Educa-tion yrs	Mean IQ (sd)	Mean Opioid Use (yrs)	Methadone use (yrs)	Mean daily methadone dose (mg)	N	Mean Age (yrs)	Sex (nM/nF)	Educa-tion (yrs)	Mean IQ (sd)	Neuropsychological Tests Measured		
Darke et al. (2000)	Australia	Fair	30	35.8	18M / 12F	11.2	91.5 (10.4)	5 (minimum)	5 (median)	78.6	30	35.2	18M / 12F	11.7	92.6 (-11.1)	WAIS-III; WMSR (PAL-I & II, VR-I & II subtests); CVLT; RCFT; COWAT; WCST		
Mintzer et al (2002)	United States	Fair	18	37.6	7M / 11F	11.8	87.4 (2.7)	15.3	3.78	67.2	21	34.9	10M / 11F	12.1	94.0 (2.8)	DSST; TMT (A&B); 2BT; GT; ST; SILS (IQ)		
Schindler et al. (2004)	Austria	Fair	15	25.8	9M / 6F	Modal attainment Junior High School	n/a	4.28	1.55	45.7			Matched for age, sex and score in MAT (intelligence)			ART-2020 (MAT; Q1; FAT; LL5; TT15; DR2; RST3)		

Abbreviations: n= Number of Participants; yrs = Years; nM/nF= Number Male/ Number Female; IQ = Intelligence quotient; sd= standard deviation; mg= milligrams; WAIS-III = Wechsler Adult Intelligence Scale; WMSR; Wechsler Memory Scale-Revised; PAL-I&II= Paired Associate Learning; VR-I&II= Visual Reproduction; CVLT= California verbal learning test; RCFT; Rey Complex Figure Test; COWAT= Controlled oral word association test; WCST= Wisconsin Card Sorting Test; SILS= Shipley Institute of Living Scale; GT= Gambling Task; DSST= Digit Symbol Substitution Test; TMT= Trail Making Test; 2BT= Two Back Test; ST= Stroop Test; WAIS-R= Wechsler Adult Intelligence Scale - Revised; BVRT= Benton Visual Retention Test; CPT= Continuous Performance Test; SOMT= Six Object Memory Test; WSLT= Word Sequence Learning Test; RRLET= Remote and Recent Life Event Test; SAVF= Semantic Association of Verbal Fluency; 3DBCM= Three Dimensional Block Construction Model; SpTW= Spot the Real World;; CBT= Corsi Block Test; CRT=Choice Reaction Time; FTT= Finger Tapping Test; TOVA= Test of Variables of Attention; SS= Stop Signal; PES= Post Error Slowing; NART= National Adult Reading Test; CGT= Cambridge Gambling Task; AGN= Affective Go/No Go; SOC= Stockings of Cambridge; AM= Austine Maze; n/a= not available; FDT= Five Digit Test; FAS= Fruits and Animals; IGT= Iowa Gambling Test; ART-2020= Act React Test System (MAT= Matrices Test (non-verbal intelligence), Q1=Attention Under Monotonous Circumstances, FAT= Test for Attention Flexibility, LL5= Test for Visual Structuring Ability, TT15=Test Measuring the Traffic-specific Perception Ability, DR2= Decision and Reaction Behaviour in a Dynamic Driving Environment, RST3= Reactive Stress Test); ART-90= Act React Test (PVT= Peripheral Vision Test, TT15=Test Measuring the Traffic-specific Perception Ability, Q1= Attention Under Monotonous Circumstances, RST3= Reactive Stress Test, DR2= Decision and Reaction Behaviour in a Dynamic Environment) KMSK= Kreek-McHugh-Schluger-Kellogg Scale.

**Table 3:** Characteristics of articles identified comparing methadone maintenance patients to healthy controls.

Rotherham-Fuller et al. (2004)	United States	Fair	18	42.3	n/a	12.2	83.8 (9.7)	0.5 (mini-mum)	0.5 (mini-mum)	61.6	19	37	n/a	13.6	92.1 (-13.2)	SILS (IQ); GT; WCST
Prosser et al. (2006)	United States	Fair	29	37.9	23M / 6F	13	8.05 (2.19)	15.1	6.44	73.8	29	34	21M / 8F	15.5	12.2 (-3.42)	WAIS-R (IQ); COWAT; ST; BVRT
Pirastu et al. (2006)	Italy	Fair	30	35	29M / 1F	8.37	85	15.5	8.3	66	21	34	14M / 7F	10.9	104 (3.39)	WAIS-III (IQ); BVRT; WCST; IGT.
Soyka et al. (2011)	Germany	Poor	24	32	16M / 8F	Modal attainment was "O" levels (n=10)	n/a	11	n/a	56	25	29.8	14M / 11F	Modal attainment was general school leaving certificate (n=9)	n/a	ART-90 (PVT; TT15; Q1; RST3; DR2)
Lin et al. (2012)	Taiwan	Fair	27	36.8	26M / 1F	10.3	n/a	13.9	1.73	36	23	34	22M / 1F	15.4	n/a	SOMT; WSLT; BVRT; RRLET; SAVF; WAIS-R (digit span, arithmetic, symbol); Reitan Proverbs Test; 3DBCM
Liao et al. (2014)	Taiwan	Fair	65	40.2	65M / 0F	8.6	n/a	14.3	0.5	45	64	36.8	64M / 0F	9.3	n/a	SS; PES
Baldacchino et al. (2014)	United Kingdom	Good	29	27.3	29M / 0F	10.6	109 (7.6)	8.8	1.3	55.8	28	24.1	28M / 0F	15.4	118 (5.1)	NART (IQ); CGT; AGN; SOC

Abbreviations: n= Number of Participants; yrs = Years; nM/nF= Number Male/Number Female; IQ = Intelligence quotient; sd= standard deviation; mg= milligrams; WAIS-III = Wechsler Adult Intelligence Scale; WMSR; Wechsler Memory Scale-Revised; PAL-I&II= Paired Associate Learning; VR-I&II= Visual Reproduction; CVLT= California verbal learning test; RCFT; Rey Complex Figure Test; COWAT= Controlled oral word association test; WCST= Wisconsin Card Sorting Test; SILS= Shipley Institute of Living Scale; GT= Gambling Test; DSST= Digit Symbol Substitution Test; TMT= Trail Making Test; 2BT= Two Back Test; ST= Stroop Test; WAIS-R= Wechsler Adult Intelligence Scale - Revised; BVRT= Benton Visual Retention Test; CPT= Continuous Performance Test; SOMT= Six Object Memory Test; WSLT= Word Sequence Learning Test; RRLET= Remote and Recent Life Event Test; SAVF= Semantic Association of Verbal Fluency; 3DBCM= Three Dimensional Block Construction Model; SptW= Spot the Real World;; CBT= Corsi Block Test; CRT=Choice Reaction Time; FTT= Finger Tapping Test; TOVA= Test of Variables of Attention; SS= Stop Signal; PES= Post Error Slowing; NART= National Adult Reading Test; CGT= Cambridge Gambling Task; AGN= Affective Go/No Go; SOC= Stockings of Cambridge; AM= Austine Maze; n/a= not available; FDT= Five Digit Test; FAS= Fruits and Animals; IGT= Iowa Gambling Test; ART-2020= Act React Test System (MAT= Matrices Test (non-verbal intelligence), Q1=Attention Under Monotonous Circumstances, FAT= Test for Attention Flexibility, LL5= Test for Visual Structuring Ability, TT15=Test Measuring the Traffic-specific Perception Ability, DR2= Decision and Reaction Behaviour in a Dynamic Driving Environment, RST3= Reactive Stress Test); ART-90= Act React Test (PVT= Peripheral Vision Test, TT15=Test Measuring the Traffic- specific Perception Ability, Q1= Attention Under Monotonous Circumstances, RST3= Reactive Stress Test, DR2= Decision and Reaction Behaviour in a Dynamic Environment) KMSK= Kreek-McHugh-Schluger-Kellogg Scale.



**Table 4:** Characteristics of articles identified comparing buprenorphine maintenance patients to healthy controls.

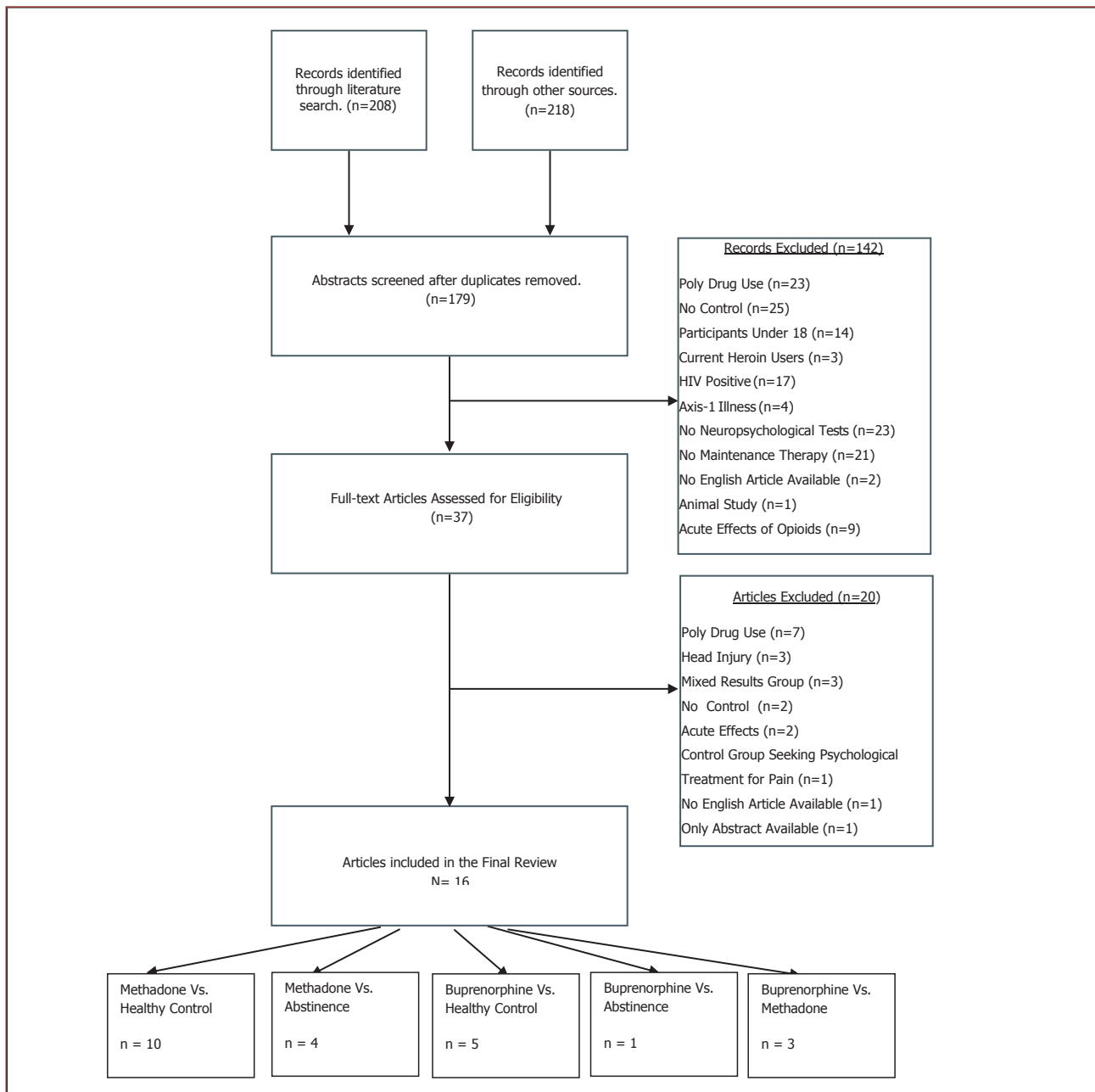
Buprenorphine Group			Healthy Controls					Neuropsychological Tests Measured								
Study	Country	Quality	n	Mean Age (yrs)	Sex (nM/nF)	Education (yrs)	Mean IQ (sd)		Mean Opioid Use (yrs)	Buprenorphine use (yrs)	Mean daily buprenorphine dose (mg)	n	Mean Age (yrs)	Sex (nM/nF)	Education (yrs)	Mean IQ (sd)
Schindler et al. (2004)	Austria	Fair	15	25	5M / 10F	Modal attainment Junior High School	n/a	3.63	0.93	10	Matched for age, sex and score in MAT (intelligence)					ART-2020 (MAT; Q1; FAT; LL5; TT15; DR2; RST3)
Pirastu et al. (2006)	Italy	Fair	18	33	17M / 1F	8.72	89.3 (-3.45)	13.3	5.4	9	21	34	14M / 7F	10.9	104 (-3.39)	WAIS-III (IQ); BVRT; WCST; IGT; RBANS
Messinis et al. (2009)	Greece	Fair	18	36.5	15M / 3F	11	n/a	12.8	0.67	6.78	34	35.7	27M / 7F	11.5	n/a	BNT; VFT; RAVLT; CTT; Ruff
Soyka et al. (2011)	Germany	Poor	22	34.2	11M / 11F	Modal attainment was general school leaving certificate (n=9) or "O" Level attainment (n=9)	n/a	11.6	0.19	10.4	25	29.8	114M / 11F	Modal attainment was general school leaving certificate (n=9)	n/a	ART-90 (PVT; TT15; Q1; RST3; DR2)
Shmygalev et al. (2011)	Germany	Fair	11	36.6	28M / 2F	n/a	n/a	n/a	5.5	7.7	90	37.1	84M / 6F	n/a	n/a	COG; DT; TAVT; VIG
Abbreviations: n= Number of Participants; yrs= Years; nM/nF= Number Male/ Number Female; IQ= Intelligence Quotient; sd= Standard Deviation; mg= Milligrams; WAIS-III= Wechsler Adult Intelligence Scale; BVRT= Benton Visual Retention Test; WCST= Wisconsin Card Scoring Task; IGT= Iowa Gambling Task; ART-2020= Act React Test System (MAT= Matrices Test (non-verbal intelligence), Q1=Attention Under Monotonous Circumstances, FAT= Test for Attention Flexibility, LL5= Test for Visual Structuring Ability, TT15=Test Measuring the Traffic-specific Perception Ability, DR2= Decision and Reaction Behaviour in a Dynamic Driving Environment, RST3= Reactive Stress Test); ART-90= Act React Test (PVT= Peripheral Vision Test, TT15=Test Measuring the Traffic-specific Perception Ability, Q1= Attention Under Monotonous Circumstances, RST3= Reactive Stress Test, DR2= Decision and Reaction Behaviour in a Dynamic Environment); BNT= Boston Naming Test; VFT= Verbal Fluency Test; RAVLT=Rey Auditory Verbal Learning Test; CTT=Color Trails Test; Ruff=Ruff Selective Attention Test; COG= Attention Test; DT=Determination Test; TAVT= Tachistoscopic Perception; VIG=Vigilance Test; n/a= Not Available																

Abbreviations: n= Number of Participants; yrs= Years; nM/nF= Number Male/ Number Female; IQ= Intelligence Quotient; sd= Standard Deviation; mg= Milligrams; WAIS-III= Wechsler Adult Intelligence Scale; BVRT= Benton Visual Retention Test; WCST= Wisconsin Card Sorting Task; IGT= Iowa Gambling Task; ART-2020= Act React Test System (MAT= Matrices Test (non-verbal intelligence), Q1=Attention Under Monotonous Circumstances, FAT= Test for Attention Flexibility, LL5= Test for Visual Structuring Ability, TT15=Test Measuring the Traffic-specific Perception Ability, DR2= Decision and Reaction Behaviour in a Dynamic Driving Environment, RST3= Reactive Stress Test); ART-90= Act React Test (PVT= Peripheral Vision Test, TT15=Test Measuring the Traffic-specific Perception Ability, Q1= Attention Under Monotonous Circumstances, RST3= Reactive Stress Test, DR2= Decision and Reaction Behaviour in a Dynamic Environment); BNT= Boston Naming Test; VFT= Verbal Fluency Test; RAVLT=Rey Auditory Verbal Learning Test; CTT=Color Trails Test; Ruff=Ruff Selective Attention Test; COG= Attention Test; DT=Determination Test; TAVT=Tachistoscopic Perception; VIG=Vigilance Test; n/a= Not Available.

**Table 5:** Characteristics of articles identified comparing buprenorphine maintenance patients to methadone maintenance patients.

Study	Country	Quality	Buprenorphine Group								Methadone Group								Neuropsychological Tests Measured
			n	Mean Age (yrs)	Sex (nM/nF)	Education (yrs)	Mean IQ (sd)	Mean Opioid Use (yrs)	Buprenorphine use (yrs)	Mean daily buprenorphine dose (mg)	n	Mean Age (yrs)	Sex (nM/nF)	Education (yrs)	Mean IQ (sd)	Mean Opioid Use (yrs)	Methadone Use (yrs)	Mean daily methadone dose (mg)	
Schindler et al. (2004)	Austria	Fair	15	25	5M / 10F	Modal attainment Junior High School	n/a	3.63	0.93	10	15	25.8	9M / 6F	Modal attainment Junior High School	n/a	4.28	1.55	45.7	ART-200 (MAT; Q1; FAT; LL5; TT15; DR2; RST3)
Pirastu et al. (2006)	Italy	Fair	18	33	17M / 1F	8.72	89.3 (-3.45)	13.28	5.4	9	30	35	29M / 1F	8.37	85	15.53	8.3	66	WAIS-III (IQ); BVRT; WCST; IGT.
Baewert et al. (2007)	Austria	Fair	20	27	12M / 8F	n/a	n/a	5.8	1.43	13.4	20	27.9	7M / 13F	n/a	n/a	6.09	1.94	52.7	ART-200 (MAT; Q1; FAT; LL5; TT15; DR2; RST3)
Soyka et al. (2011)	Germany	Poor	22	34.2	11M / 11F	Modal attainment was general school leaving certificate (n=9) or "O" Level attainment (n=9)	n/a	11.6	0.19	10.4	24	32	16M / 8F	Modal attainment was "O" levels (n=10)	n/a	11	0.4	56	ART-90 (PVT; TT15; Q1; RST3; DR2)

Abbreviations: n=Number of Participants; yrs= Years; nM/nF= Number Males/Number Females; IQ= Intelligence Quotient; sd= Standard Deviation; mg=Milligrams; ART-200= Act React Test System (MAT= Matrices Test (non-verbal intelligence), Q1=Attention Under Monotonous Circumstances, FAT= Test for Attention Flexibility, LL5= Test for Visual Structuring Ability, TT15=Test Measuring the Traffic-specific Perception Ability, DR2= Decision and Reaction Behaviour in a Dynamic Driving Environment, RST3= Reactive Stress Test); WAIS-III= Wechsler Adult Intelligence Scale; BVRT= Benton Visual Retention Test; WCST= Wisconsin Card Sorting Test; IGT= Iowa Gambling Test; ART-90= Act React Test (PVT= Peripheral Vision Test, TT15=Test Measuring the Traffic-specific Perception Ability, Q1= Attention Under Monotonous Circumstances, RST3= Reactive Stress Test, DR2= Decision and Reaction Behaviour in a Dynamic Environment); n/a= Not Available.



**Figure 1. QUORUM**

were the neurocognitive assessments of 279 methadone maintained individuals from 10 published articles and 84 individuals maintained on buprenorphine compared to healthy controls from 5 published papers [34], although one article is included in each comparison in the table as it compared healthy controls against methadone and buprenorphine and in addition a direct comparison between methadone and buprenorphine groups.

The papers included are shown in table 6.

### 13.5. Neurocognitive impairments between groups

In the articles directly comparing patients on ORT treatment [1, 25, 34], all except one domain (cognitive impulsivity) showed no significant differences between cognitive functioning in methadone and buprenorphine treated individuals.

#### 13.5.1. Cognitive impulsivity

Buprenorphine maintained individuals scored significantly better ( $p < 0.05$ ) on measures of cognitive impulsivity than methadone maintained individuals in all three selected studies [1, 25, 34]. This is also supported by all other selected studies measuring this



**Table 6.** Articles included, comparison groups and neurocognitive domain

Article	Outcome Group and Number (n)	Control Group Type and Number (n)	Intelligence	Short Term Memory	Long Term Memory	Attention	Cognitive Flexibility	Cognitive Impulsivity	Motor Impulsivity	Non Planning Impulsivity
Methadone Maintenance Papers										
Darke et al. 2000	30	30	↓ - WAIS-III	↓ - WMSR, CVLT,	↓ - WSMR, CVLT	↓ - WAIS-III	↓ - COWAT, WCST	n/a	n/a	↓ - RCFT (Copy)
Mintzer et al. 2002	18	21	— - SILS	— - 2BT	n/a	↓ - DSST	↓ - TMT	↓ - GT	n/a	n/a
Rotherham-Fuller et al. 2004	18	19	— - SILS	n/a	n/a	n/a	— - WCST	↓ - GT	n/a	n/a
Schindler et al. 2004	15	Matched CON (See Demographic Table)	— - MAT	n/a	n/a	↓ - DR2, Q1 — - FAT	□ - LL5, TT15	↓ - DR2	n/a	n/a
Prosser et al. 2006	23	29	↓ - WAIS-III	↓ - BVRT	n/a	— - ST	— - COWAT	n/a	n/a	n/a
Pirastu et al. 2006	30	21	↓ - WAIS-III	↓ - BVRT	n/a	n/a	↓ - WCST (errors)	↓ - GT	n/a	n/a
Soyka et al. 2011	24	25	n/a	↓ - TT15	n/a	— - PVT ↓ - Q1 (correct)	↓ - TT15	↓ - DR2	↓ - RST-3 (Phase 1) ↓ - RST-3 (Phase 2) ↓ - RST-3 (Phase 3)	n/a
Lin et al. 2012	27	23	— - WAIS-III	— - BVRT, SOMET, WSLT, RRLET, SAVF	— - RRLET, SAVF	— - WAIS-R	n/a	n/a	n/a	n/a

Abbreviations: n= Number of Participants; MMT= Methadone Maintenance Programme; CON= Healthy Control; ABST= Protracted Abstinence; BUP= Buprenorphine Maintenance; WAIS-III= Wechsler Adult Intelligence Scale; SILS= Shipley Institute of Living Scale; MAT = Matrices Test; NART= National Adult Reading Test; WSMR= Wechsler Memory Scale - Revised; RCFT= Rey Complex Figure Test; 2BT= Two Back Test; BVRT= Benton Visual Retention Test; SOMT= Six Object Memory Test; WSLT= Word Sequence Learning Test; RRLET= Remote and Recent Life Event Test; SAVF= Semantic Association of Verbal Fluency; CVLT= California Verbal Learning Test; RAVLT= Rey Auditory Verbal Learning Test; RBANS= Repeatable Battery for the Assessment of Neurological Status; FAS= Fruits and Animals; DSST= Digit Symbol Substitution Test; ST= Stroop Test; CPT=Continuous Performance Test; WAIS-R Wechsler Adult Intelligence Scale - Revised; SS= Stop Signal; PES= Post Error Slowing; FDT= Five Digit Test; Ruff= Ruff Selective Attention Test; CTT= Color Trails Test; COG= Attention Test; VIG= Vigilance Test; COWAT= Controlled Oral Word Association Test; WCST= Wisconsin Card Sorting Task; TMT= Trail Making Test; BNT= Boston Naming Test; VFT= Verbal Fluency Test; TAVT= Tachistoscopic Perception; GT= Gambling Test; CGT= Cambridge Gambling Test; FTT= Finger Tapping Test; AGN= Affective Go/No Go; DT=Determination Test; RCFT= Rey Complex Figure Test; AM=Austine Maze; SOC=Stockings of Cambridge; ART-2020= Act React Test System (MAT= Matrices Test (non-verbal intelligence), Q1=Attention Under Monotonous Circumstances, FAT= Test for Attention Flexibility, LL5= Test for Visual Structuring Ability, TT15=Test Measuring the Traffic-specific Perception Ability, DR2= Decision and Reaction Behaviour in a Dynamic Driving Environment, RST3= Reactive Stress Test); ART-90= Act React Test (PVT= Peripheral Vision Test TT15=Test Measuring the Traffic-specific Perception Ability, Q1= Attention Under Monotonous Circumstances, RST3= Reactive Stress Test, DR2= Decision and Reaction Behaviour in a Dynamic Environment); BNT= Boston Naming Test; VFT= Verbal Fluency Test; RAVLT=Rey Auditory Verbal Learning Test; CTT=Color Trails Test; Ruff=Ruff Selective Attention Test; COG= Attention Test; DT=Determination Test; TAVT=Tachistoscopic Perception; VIG=Vigilance Test; n/a= Not Available.

**Table 6.** Articles included, comparison groups and neurocognitive domain

Liao et al. 2014	65	64	n/a	n/a	— - SS, - PES	n/a	n/a	n/a	n/a
Baldacchino et al. 2014	29	28	- NART	n/a	n/a	n/a	- CGT	— - AGN	- SOC
Buprenorphine Papers									
Schindler et al. 2004	15	Matched CON (See Demo-graphic Table)	— - MAT	n/a	n/a	- DR2, FAT - Q1 (% incorrect)	- LL5, TT15	— - DR2	n/a
Pirastu et al. 2006	18	21	- WAIS-III	- BVRT	n/a	n/a	— - WCST	— - GT	n/a
Messinis et al. 2009	18	34	n/a	- RAVLT, RBANS	n/a	- Ruff - CTT2	- BNT, VFT	n/a	n/a
Soyka et al. 2011	22	25	n/a	- TT15	n/a	— - PVT - Q1 (Correct)	- TT15	— - DR2	- RST-3 (Phase 1) - RST-3 (Phase 2) — - RST-3 (Phase 3)
Shmygalev et al. 2011	11 (Per-protocol)	90	n/a	n/a	n/a	— - COG	— - TAVT	n/a	- DT (Mean Reaction Time)
Comparison Group (n)									
Pirastu et al. 2006	18	30	— - WAIS-III	— - BVRT	n/a	n/a	— - WCST	- GT	n/a
Baewert et al. 2007	20	20	— - MAT	n/a	n/a	- DR2 — - Q1, FAT	- LL5, TT15	- DR2	— - RST3
Key:	Significantly Lower Score (p<0.05), Significant Higher Score (p<0.05), No Significant Difference in score. (Outcome Group vs. Control or Comparison Group)								

Abbreviations: n= Number of Participants; MMT= Methadone Maintenance Programme; CON= Healthy Control; ABST= Protracted Abstinence; BUP= Buprenorphine Maintenance; WAIS-III= Wechsler Adult Intelligence Scale; SILS= Shipley Institute of Living Scale; MAT = Matrices Test; NART= National Adult Reading Test; WSMR= Wechsler Memory Scale - Revised; RCFT= Rey Complex Figure Test; 2BT= Two Back Test; BVRT= Benton Visual Retention Test; SOMT= Six Object Memory Test; WSLT= Word Sequence Learning Test; RRLET= Remote and Recent Life Event Test; SAVF= Semantic Association of Verbal Fluency; CVLT= California Verbal Learning Test RAVLT= Rey Auditory Verbal Learning Test; RBANS= Repeatable Battery for the Assessment of Neurological Status; FAS= Fruits and Animals; DSST= Digit Symbol Substitution Test; ST= Stroop Test; CPT=Continuous Performance Test; WAIS-R Wechsler Adult Intelligence Scale - Revised; SS= Stop Signal; PES= Post Error Slowing; FDT= Five Digit Test; Ruff= Ruff Selective Attention Test; CTT= Color Trails Test; COG= Attention Test; VIG= Vigilance Test; COWAT= Controlled Oral Word Association Test; WCST= Wisconsin Card Sorting Task; TMT= Trail Making Test; BNT= Boston Naming Test; VFT= Verbal Fluency Test; TAVT= Tachistoscopic Perception; GT= Gambling Test; CGT= Cambridge Gambling Test; FTI= Finger Tapping Test; AGN= Affective Go/No Go; DT=Determination Test; RCFT= Rey Complex Figure Test; AM=Austine Maze; SOC=Stockings of Cambridge; ART=2020= Act React Test System (MAT= Matrices Test (non-verbal intelligence), Q1=Attention Under Monotonous Circumstances, FAT= Test for Attention Flexibility, LL5= Test for Visual Structuring Ability, TT15=Test Measuring the Traffic-specific Perception Ability, DR2= Decision and Reaction Behaviour in a Dynamic Driving Environment, RST3= Reactive Stress Test); ART-90= Act React Test (PVT= Peripheral Vision Test TT15=Test Measuring the Traffic-specific Perception Ability, Q1= Attention Under Monotonous Circumstances, RST3= Reactive Stress Test, DR2= Decision and Reaction Behaviour in a Dynamic Environment); BNT= Boston Naming Test; VFT= Verbal Fluency Test; RAVLT=Rey Auditory Verbal Learning Test; CTT=Color Trails Test; Ruff=Ruff Selective Attention Test; COG= Attention Test; DT=Determination Test; TAVT=Tachistoscopic Perception; VIG=Vigilance Test; n/a= Not Available.

cognitive domain and compared with healthy controls [3, 23, 25, 28, 30, 34]. There was however no significant difference found in cognitive impulsivity between buprenorphine maintained individuals and healthy controls [25, 30, 34].

### *13.5.2. Cognitive flexibility*

In the three studies directly comparing methadone to buprenorphine treatment there were no significant differences in cognitive flexibility scores reported. However cognitive flexibility was more frequently reported as significantly impaired ( $p < 0.05$ ) in patients maintained on methadone, than those on buprenorphine when compared to healthy controls. Four of the ten selected studies [8, 23, 25, 34], showed impairment for methadone maintained individuals compared to healthy control. In comparison only one of five studies that reviewed cognitive flexibility in buprenorphine treated individuals identified impairment [34], with the other 4 papers finding no impairment in this domain in comparison to healthy controls.

### *13.5.3. Motor impulsivity*

In the three papers conducting the direct comparison between methadone treatment and buprenorphine treatment, there were no reported differences in the motor impulsivity. However in the studies looking at comparison to healthy controls, both methadone and buprenorphine treated cohorts exhibited impairments in motor impulsivity when compared to healthy controls [32, 34].

### *13.5.4. Attention*

One measure (DR2) in relation to the attention domain found buprenorphine individuals were less impaired than methadone in the papers comparing treatments against each other directly [1]. However the same paper found no significant difference on two other assessments of attention (Q1 & FAT). Soyka [34] also found no significant difference in attention test scores when comparing methadone to buprenorphine. Five articles that compared methadone to healthy controls identified a significant impairment in attention [8, 19, 23, 30, 34] with four buprenorphine comparison papers showed an impairment ( $p < 0.05$ ) in the attention domain [30, 21, 32, 34].

### *13.5.5. Short term memory*

From the two direct comparison articles between methadone and buprenorphine cohorts that reported on Short Term Memory, there was no significant difference found [25, 34]. Short term memory was sig-

nificantly impaired ( $p < 0.05$ ) relative to healthy controls in both methadone and buprenorphine cohorts. Four of the identified studies found a significant impairment ( $p < 0.05$ ) when methadone maintained individuals were compared to healthy controls [3, 8, 25, 27]. Three of the studies comparing buprenorphine to healthy controls showed significant impairment ( $p < 0.05$ ) in short term memory [21, 25, 34].

## **14. Discussion**

### *14.1. Summary of findings*

Buprenorphine maintained individuals demonstrate reduced impairment of cognitive impulsivity compared to those maintained on methadone. This was the most reliable conclusion drawn from the results as a significant difference was observed both in papers directly comparing methadone with buprenorphine and comparisons with control groups.

The attention domain shows that buprenorphine patients are less impaired than patients on methadone in the direct comparative studies. However, in the articles comparing methadone or buprenorphine to healthy controls, both treatments were shown to cause equal impairment. The differences between buprenorphine and methadone in relation to the attention domain could be due to the increased sedation experienced with a full opioid agonist in comparison to a partial agonist [29].

Cognitive flexibility was reported to be significantly less impaired ( $p < 0.05$ ) in buprenorphine maintained cohorts than methadone when compared to healthy controls. However this was not replicated in articles that directly compare the domain between methadone or buprenorphine maintained patients.

### *14.2. Significance*

As the literature search demonstrated, using the strict criteria employed in this review, there is little evidence available currently to directly compare both buprenorphine and methadone maintenance therapies in relation to neurocognitive function. The articles that have been included highlights that there are differences between treatments and these may provide benefits for patients increasing the success of their treatment. However there is a lack of consistency in the tests employed in the research to date.

### *14.3. Strength and Limitations*

The literature search found no Randomised Control Trials (RCTs) and all articles included are case-control studies. The lack of randomized blinded studies limits result reliability due to the possibility of increased bias [15]. Due to methodological difficulties, patients were not blinded to their interventional group with only two articles used a single blinded methodology [1, 30].

Articles were excluded if they included individuals affected by simultaneous illicit drug use or medication that might affecting neurocognitive function to minimise the effect of compounding factors. Most articles used different definitions of simultaneous drug use, showing a differing application of exclusion criteria between papers. Some conducted urinalysis over a period of months and others allowed for positive urine test if the individual was not experiencing acute effects. The most commonly identified additional substance was benzodiazepines, which are known to have effects on neurocognitive function [8, 28, 34, 37]. These mitigate the acute effects of benzodiazepines on the result of the neurocognitive tests and question the cause of any reported neurocognitive impairments in these studies. This becomes more important when comparing buprenorphine due to the limited number of papers available covering this area. The less robust exclusion criteria used in Soyka's [34] paper reduces the reliability of the results from this study. The results mirror those from the other three papers making this comparison [1, 25, 30], reducing the likelihood that benzodiazepine use caused these results. However it must be noted that benzodiazepine use is frequent amongst active heroin users, as well as those enrolled in maintenance opioid agonist replacement programmes. [16]. None of the studies considered the potential neurocognitive sequelae of chronic nicotine and/or cannabis use in this treatment seeking population.

The selected articles sample size lack consistency across the five studies investigating buprenorphine. They included 84 individuals, contrasting to 279 methadone maintained individuals across 10 selected studies. Potential root causes of this difference in articles identified are; (a) the limited period of time that buprenorphine preparations have been licensed for use in opioid dependence (mid-1990s for buprenorphine as opposed to methadone's availability since the 1960s) and (b) methadone being the preferential use of methadone as a first line treatment to opioid dependence [39].

The published articles are using small numbers studying individuals attending diverse treatment sys-

tems. A large degree of heterogeneity existed between studies, e.g. mean opioid use ranged from six months to over fifteen years between methadone cohorts [25, 28]. Other demographics followed similar trends, e.g. mean buprenorphine dose ranged from 6.78mg [21] to 13.4mg [1]. There were significant differences reported between comparable populations within individual selected studies. There were discrepancies in age, gender and educational attainment between populations [3, 20, 25, 27]. Significant differences in the completed educational years could have a profound effect on the neurocognitive test scores reported by these groups in the intelligence domain. Matching controls based on an estimate of their pre-morbid intelligence (IQ) will reduce this bias.

The time between administration of the maintenance dose and conducting the neurocognitive assessments needs to be considered as variations in the time delay may have different impairments on neurocognitive function due to the acute sedative effects of the treatment modality used [5]. One paper analysed the difference in scores between peak levels (1.5 hours after administration) and trough levels (20 hours after administration) for both methadone and buprenorphine. The combined results showed that individuals at trough levels performed significantly worse on the RST3 assessment of motor impulsivity [1]. In this review, the majority of studies included did not specify the time between administration of the last dose and neuropsychological test which impacts on repeatability and result interpretation. The large variation in duration of action means that individuals maintained on different opioids may experience the onset of withdrawal symptoms, at different times which may affect the neurocognitive assessment. Thus, if the assessment is conducted at the same time post administration; the methadone maintained cohort may collectively experience withdrawal symptoms earlier than the buprenorphine maintained cohort in direct comparison studies. Some studies screened for opioid withdrawal at the time of testing ensuring participants were not in withdrawal [30, 37], whilst others conducted assessments well within the duration of action of treatments [3, 17].

Multiple different cognitive domains are described and used in the literature. For the purposes of this enquiry the domains set out by Baldacchino et al. [4] were used.

Until a standardised system of domains and assessment exists there will always be discrepancies and variations in the tests used and subsequent result classification, damaging the integrity of conclusions



drawn from these studies

It is important to consider compounding factors affecting neurocognition, including head injury, alcohol use and overdose. Regression analysis was used by some papers to correct for variations of these factors. The rigorous inclusion criteria applied to papers is a strength of the review, and provides clear results comparing methadone/buprenorphine to a control or each other. This allowed a large array of data to be extracted from included papers. The majority of papers did not directly compare methadone to buprenorphine and further research into this area could address this factor.

Decreased neurocognitive test scores for both treatments were demonstrated in comparison to healthy controls. The comparison of each treatment option against healthy controls allows some inference to the effects of each treatment on the neurocognitive impairments experienced. The differences observed between the neurocognitive impairment and the prescribed treatment modality validates the need for further direct comparison research between the treatment options.

#### 14.4. Clinical relevance

The relevance of this review can be demonstrated in the application to driving ability. It is illegal to drive whilst impaired under the influence of any drug. England and Wales have a blood concentration limit for methadone of 500mcg/L of blood [9]. Buprenorphine has no defined concentration limit. Therefore if supported by further research and one treatment is proven to provide improved scores this could influence treatment choice. Therefore this review helps to identify better the current knowledge base when making clinical decisions on choice of opioid used for ORT to improve road safety and treatment retention.

The effect on neurocognitive function could be extrapolated to other functions and abilities and assist in making treatment choices for patients which are better suited and many patients report to a “clear head” with buprenorphine as opposed to “clouding” with methadone [14, 29, 35]. This subjectively based reduced neurocognitive impairment would be of greater benefit to the patients recovery and treatment on the grounds of the limited evidence identified. E.g. decreased neurocognitive impairment would be preferential for patients who are currently employed or actively seeking employment, those with a carers’ role for either children or physically unwell individuals or those needing to be able to drive or operate

heavy machinery. However for some patients a degree of cognitive impairment may be beneficial. E.g. states of increased boredom and “problematic thoughts that can increase the risk of relapse” [35]. This observation should be taken with extreme caution as this systematic review has highlighted the urgent need to conduct methodologically sound, unbiased and well powered studies to be able to identify better significant correlation between observed neurocognitive impairments and type of agonist opioid treatment used with clinical practice.

## 15. Conclusions

In conclusion, this systematic review of published literature into the neurocognitive function of individuals on methadone or buprenorphine maintenance treatment shows that there are fewer than expected reports of impaired neurocognitive function when patients are prescribed buprenorphine in comparison to methadone. There is a need for more rigorous and larger well matched longitudinal studies to reduce the variances caused due to opioid withdrawal influencing the result and to measure neurocognitive impairment of pharmacologically maintained individuals over time.

## References

1. Baewert A., Gombas W., Schindler S. D., Peternell-Moelzer A., Eder H., Jagsch R., Fischer G. (2007): Influence of peak and trough levels of opioid maintenance therapy on driving aptitude. *Eur Addict Res.* 13(3): 127-135.
2. Bahrick H. P., Bahrick P. O., Wittlinger R. P. (1975): Fifty Years of Memory for Names and Faces: A Cross-Sectional Approach. *J Exp Psychol Gen.* 104(1): 54-75.
3. Baldacchino A., Balfour D. J., Matthews K. (2015): Impulsivity and opioid drugs: differential effects of heroin, methadone and prescribed analgesic medication. *Psychol Med.* 45(6): 1167-1179.
4. Baldacchino A., Balfour D. J., Passetti F., Humphris G., Matthews K. (2012): Neuropsychological consequences of chronic opioid use: a quantitative review and meta-analysis. *Neurosci Biobehav Rev.* 36(9): 2056-2068.
5. Baldacchino A., Armanyous M., Balfour D. J., Humphris G., Matthews K. (2017): Neuropsychological functioning and chronic methadone use: A systematic review and meta-analysis. *Neurosci Biobehav Rev.* 73: 23-38.
6. Buttner A., Mall G., Penning R., Weis S. (2000): The neuropathology of heroin abuse. *Forensic Sci Int.* 113(1-3): 435-442.
7. Cunha-Oliveira T., Rego A. C., Oliveira C. R. (2008): Cellular and molecular mechanisms involved in the



- neurotoxicity of opioid and psychostimulant drugs. *Brain Res Rev.* 58(1): 192-208.
8. Darke S., Sims J., McDonald S., Wickes W. (2000): Cognitive impairment among methadone maintenance patients. *Addiction.* 95(5): 687-695.
  9. Department for Transport (2013): Drug Driving. Available at: <https://www.gov.uk/government/collections/drug-driving#table-of-drugs-and-limits> [Accessed April 6, 2016].
  10. Enevoldson T. P. (2004): Recreational drugs and their neurological consequences. *J Neurol Neurosurg Psychiatry.* 75 Suppl 3: iii9-15.
  11. Ersche K. D., Sahakian B. J. (2007): The neuropsychology of amphetamine and opiate dependence: implications for treatment. *Neuropsychol Rev.* 17(3): 317-336.
  12. Fine P. G., Portenoy R. K. (2004): A Clinical Guide to Opioid Analgesia Vendome Group Healthcare Division, New York, NY, USA.
  13. Gould T. J. (2010): Addiction and cognition. *Addict Sci Clin Pract.* 5(2): 4-14.
  14. Hill D., Conroy S., Afzal A., Lang D., Steele S., Campbell D. (2015): A comparison of methadone and buprenorphine-naloxone as opioid substitution therapy: the patient perspective in NHS Lanarkshire. *J Subst Abuse.* 20(3): 168-177.
  15. Hróbjartsson A., Emanuelsson F., Skou Thomsen A. S., Jørgen Hilden Stig Brorson J. (2014): Bias due to lack of patient blinding in clinical trials. A systematic review of trials randomizing patients to blind and nonblind sub-studies. , 43(4), 1272-1283. *Int J Epidemiol.* 43(4): 1272-1283.
  16. Jones J. D., Mogali S., Comer S. D. (2012): Polydrug abuse: a review of opioid and benzodiazepine combination use. *Drug Alcohol Depend.* 125(1-2): 8-18.
  17. Levy-Gigi E., Keri S., Shapiro A. R., Sason A., Adelson M., Peles E. (2014): Methadone maintenance patients show a selective deficit to reverse positive outcomes in drug-related conditions compared to medication free prolonged opiate abstinence. *Drug Alcohol Depend.* 144: 111-118.
  18. Lezak M. D. (1983): Neuropsychological Assessment. Oxford University Press, Oxford, UK.
  19. Liao D. L., Huang C. Y., Hu S., Fang S. C., Wu C. S., Chen W. T., Lee T. S., Chen P. C., Li C. S. (2014): Cognitive control in opioid dependence and methadone maintenance treatment. *PLoS One.* 9(4): e94589.
  20. Lin W. C., Chou K. H., Chen H. L., Huang C. C., Lu C. H., Li S. H., Wang Y. L., Cheng Y. F., Lin C. P., Chen C. C. (2012): Structural deficits in the emotion circuit and cerebellum are associated with depression, anxiety and cognitive dysfunction in methadone maintenance patients: a voxel-based morphometric study. *Psychiatry Res.* 201(2): 89-97.
  21. Messinis L., Lyros E., Andrian V., Katsakiori P., Panagis G., Georgiou V., Papathanasopoulos P. (2009): Neuropsychological functioning in buprenorphine maintained patients versus abstinent heroin abusers on naltrexone hydrochloride therapy. *Hum Psychopharmacol.* 24(7): 524-531.
  22. Miller G. A. (1956): The magical number seven plus or minus two: some limits on our capacity for processing information. *Psychol Rev.* 63(2): 81-97.
  23. Mintzer M. Z., Stitzer M. L. (2002): Cognitive impairment in methadone maintenance patients. *Drug Alcohol Depend.* 67(1): 41-51.
  24. Nih (2014): Quality Assessment of Case-Control Studies. Available at: <http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/case-control> [Accessed March 2, 2016].
  25. Pirastu R., Fais R., Messina M., Bini V., Spiga S., Falconieri D., Diana M. (2006): Impaired decision-making in opiate-dependent subjects: effect of pharmacological therapies. *Drug Alcohol Depend.* 83(2): 163-168.
  26. Prosser J., Cohen L. J., Steinfeld M., Eisenberg D., London E. D., Galynker, Ii (2006): Neuropsychological functioning in opiate-dependent subjects receiving and following methadone maintenance treatment. *Drug Alcohol Depend.* 84(3): 240-247.
  27. Prosser J., London E. D., Galynker, Ii (2009): Sustained attention in patients receiving and abstinent following methadone maintenance treatment for opiate dependence: performance and neuroimaging results. *Drug Alcohol Depend.* 104(3): 228-240.
  28. Rotheram-Fuller E., Shoptaw S., Berman S. M., London E. D. (2004): Impaired performance in a test of decision-making by opiate-dependent tobacco smokers. *Drug Alcohol Depend.* 73(1): 79-86.
  29. Royal College of General Practitioners (2004): Guidance for the use of substitute prescribing in the treatment of opioid dependence in primary care. RCGP, UK.
  30. Schindler S. D., Ortner R., Peterzell A., Eder H., Opgenoorth E., Fischer G. (2004): Maintenance therapy with synthetic opioids and driving aptitude. *Eur Addict Res.* 10(2): 80-87.
  31. Shipley W. C. (1940): A Self-Administering Scale for Measuring Intellectual Impairment and Deterioration. *The Journal of Psychology.* 9(2): 371-377.
  32. Shmygalev S., Damm M., Weckbecker K., Berghaus G., Petzke F., Sabatowski R. (2011): The impact of long-term maintenance treatment with buprenorphine on complex psychomotor and cognitive function. *Drug Alcohol Depend.* 117(2-3): 190-197.
  33. Skrabalova J., Drastichova Z., Novotny J. (2013): Morphine as a Potential Oxidative Stress-Causing Agent. *Mini-Reviews in Organic Chemistry.* 10(4): 367-372.
  34. Soyka M., Limmer C., Lehnert R., Koller G., Martin G., Kufner H., Kagerer S., Habertur A. (2011): A comparison of cognitive function in patients under maintenance treatment with heroin, methadone, or buprenorphine and healthy controls: an open pilot study. *Am J Drug Alcohol Abuse.* 37(6): 497-508.
  35. Tanner G. R., Bordon N., Conroy S., Best D. (2011): Comparing methadone and Suboxone in applied

- treatment settings: the experiences of maintenance patients in Lanarkshire. *J Subst Use*. 16(3): 171-178.
36. Tolomeo S., Gray S., Matthews K., Steele J. D., Baldacchino A. (2016): Multifaceted impairments in impulsivity and brain structural abnormalities in opioid dependence and abstinence. *Psychol Med*. 46(13): 2841-2853.
  37. Verdejo A., Toribio I., Orozco C., Puente K. L., Perez-Garcia M. (2005): Neuropsychological functioning in methadone maintenance patients versus abstinent heroin abusers. *Drug Alcohol Depend*. 78(3): 283-288.
  38. Wechsler D. (1997): WAIS-III administration and scoring manual. Psychological Corporation, New York, NY, USA.
  39. Whelan P. J., Remski K. (2012): Buprenorphine vs methadone treatment: A review of evidence in both developed and developing worlds. *J Neurosci Rural Pract*. 3(1): 45-50.

#### *Acknowledgements*

The authors would like to acknowledge the Medical School at the University of St Andrews for their support in preparing the article.

#### *Role of the funding source*

Financial support for the implementation of this review was provided by internal funds.

#### *Contributors*

The authors contributed equally to this review.

#### *Conflict of interest*

Authors declared no conflict of interest.

*Received December 7, 2017 - Accepted March 1, 2018*

